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Strategic and Statistical Considerations on the QT Assessment of Volasertib

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Abstract

Volasertib is a selective cell cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting Polo-like kinase (Plk). A potential for prolonged QT intervals was indicated with volasertib in preclinical studies and preliminary clinical data. As a result, electrocardiograms (ECGs) have been collected in all volasertib clinical trials to monitor potential cardiac effects. This article describes strategic and statistical methods prospectively planned to perform an integrated analysis of ECG data from available trials to evaluate volasertib's effect on cardiac repolarization, as reflected by changes in the duration of QT interval and other ECG-related endpoints. Methods to effectively cope with heterogeneity between trials (ie, differences in study designs) are discussed. These strategies may be useful for other investigational drugs for which QT risk assessment is required, but a thorough QT/QTc trial is not feasible, resulting in the need for an alternative approach. Volasertib therapy relevantly prolonged adjusted mean QTcF change from administration baseline following the first and subsequent infusions. The integrated analysis revealed that the volasertib effects on the mean QTc changes from baseline were transient and had resolved at 24 hours after start of the first infusion. There was no evidence for a long-term impact on the QTcF interval following multiple infusions with volasertib.

Keywords

Volasertib, Polo-like kinase inhibitor, oncology, QTc prolongation, integrated ECG analysis

Introduction

Over the past 5 to 10 years, it has become evident that an increasing number of drugs used in the treatment of cancer are associated with a prolongation of the QT interval corrected for heart rate (QTc), an indicator of increased risk of developing torsade de pointes.[1] A thorough QT/QTc trial (TQT trial) performed in healthy volunteers according to the International Conference on Harmonisation (ICH) E14 guidelines[2] is rarely feasible during the development of anticancer drugs, as typical principles of the TQT study may be either impractical or unethical. First, the administration of an anticancer agent at a dose that is significantly higher than the recommended therapeutic dose in healthy volunteers without malignancy would expose them to unacceptable adverse effects. Second, QT studies in a target patient population with diseases that may respond to a study drug may not be appropriate if the need for treatment excludes placebo treatment.[3] Nevertheless, it is expected by regulatory authorities that appropriate clinical QT evaluations based on preclinical information and feasibility considerations are also conducted in oncologic drug development.[4]

Volasertib is a low-molecular-weight, highly potent, and specific inhibitor of Polo-like kinase (Plk) that is administered intravenously. The serine/threonine kinase Plk1 controls several key steps in the passage of cells through mitosis. Inhibition of Plk1 results in cell cycle arrest with subsequent induction of apoptosis, making Plk1 an attractive target for novel therapeutic approaches in cancer.[5] Volasertib has shown antitumor activity in early clinical trials.[6-8] Pharmacokinetics of volasertib was determined in patients receiving 1- or 2-hour continuous intravenous infusions over a broad range of doses. Briefly, volasertib exhibited a multi-exponential pharmacokinetic behaviour with fast distribution after the end of infusion followed by several slower elimination phases and a half-life of approximately 113 hours.

Preclinical studies, as well as preliminary data from clinical studies, indicated a potential for prolonged QT/QTc.[9] QT/QTc assessment by conducting a formal, positive-controlled thorough QT/QTc trial was not considered feasible for the reasons given above; therefore, it was imperative to find an alternative approach.[3,7] Based on the potential of a QT prolonging effect, electrocardiogram (ECG) monitoring has been performed in all

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clinical trials of volasertib. This article describes strategic and statistical considerations prospectively planned to perform an integrated analysis of ECG data from all available trials to evaluate the effect of volasertib on cardiac repolarization, as reflected by changes in the duration of QTc interval and other ECG-related endpoints. These considerations may be useful for other investigational drugs for which QT risk assessment is required but a TQT study is not feasible and, therefore, an alternative approach is needed. This approach requires broadly similar ECG monitoring (including timing of ECG assessments within treatment cycles) across different trials and a common definition of primary and secondary ECG endpoints.

Materials and Methods

All analyses including endpoints and pooling strategy were prospectively planned.

Alternative Approach

Nine phase 1 trials, 4 phase 2 trials, and 1 phase 3 trial evaluating volasertib in adult patients with cancer (including acute myeloid leukemia, non–small cell lung cancer, ovarian carcinoma, urothelial carcinoma, and other types of solid tumors) were either completed or still ongoing. Each trial included intensive ECG monitoring following the administration of volasertib as a monotherapy or in combination with other anticancer compounds, thereby providing a relevant amount of ECG data. The ECG data from all studies were pooled to build an adequate data set to assess the potential effect of volasertib on the QT interval. This data set includes ECG data for approximately 1000 patients treated with volasertib. A meta-analysis based on pooled individual patient data (also referred to as integrated analysis) was planned with the objective to prospectively assess the proarrhythmic risk after treatment with volasertib. The magnitude of ECG-related effects following intravenous volasertib infusions of 1- and 2-hour duration was estimated with adequate precision, thereby enabling a risk-benefit assessment and appropriate safety information. Some heterogeneity between trials was unavoidable, mainly due to different primary objectives entailing different designs of the trials, and it is described below how to deal prospectively with the heterogeneous components.

ECG and Pharmacokinetic Assessments

All trials included in the analysis had triplicate ECG recordings at multiple time points immediately followed by pharmacokinetic blood sampling across a wide variety of dosage regimens. All ECGs were recorded digitally with ECG equipment provided by an ECG core laboratory. The core laboratory measured the cardiac intervals and provided a standardized, morphologic evaluation. Time points at which ECGs were recorded commonly across all trials were selected for inclusion in the analysis. In particular, triplicate ECGs were collected prior to the first infusion (baseline), at the end and 1 hour after the end of infusion, and approximately 6 hours and 24 hours following the start of the first infusion in phase 1-2 trials. For subsequent infusions in phase 1-2 trials and for all infusions in the phase 3 trial, triplicate ECGs were collected only prior to the infusion (baseline) and at the end of infusion (coinciding with peak plasma concentration).

Analysis Strategies

Due to the deviations in the measurement schedule applied to the first and all subsequent infusions, 2 basic analysis strategies were considered for the integrated analysis. One analysis is restricted to the ECG data recorded during the first infusion and includes all available time points collected over the period of 24 hours following the start of the first infusion, that is, the focus is the evaluation of the time profile following 1 single infusion of volasertib (phase 3 trial not included). The second analysis includes data from all available infusions but is restricted to the time point end of infusion, where the largest effect is expected. The intention of this analysis is to evaluate if there is a long-term impact of multiple infusions of volasertib on the ECG endpoints.

Endpoints and Variables

Apart from the primary ECG variable, QT interval corrected with Fridericia's formula (QTcF interval), further variables comprise the QT interval corrected with Bazett's formula (QTcB interval), heart rate (HR), the uncorrected QT interval, the PR interval, and the QRS complex duration. In addition to the correction formulae defined by Fridericia and Bazett, a population correction factor was estimated from baseline QT and RR data separately for each treatment group. This correction factor was used to derive the QT interval corrected according to baseline data (QTcN).

Based on the 2 analysis strategies, the following 2 endpoints were prespecified

- Change in QTcF interval between baseline and multiple time points following the first intravenous infusion of volasertib.
- Change in QTcF interval from baseline to end of infusion following all infusions of volasertib.

Both endpoints were also derived for all other ECG variables described above.

Dosing Regimen

Volasertib was administered as 1- or 2-hour continuous intravenous infusions in different schedules (on day 1 of a 3-week cycle, on days 1 and 8 of a 3-week cycle, on days 1 and 15 of a 4-week cycle) and at many different doses from 12 to 550 mg. As plasma concentration levels decrease rapidly after the end of infusion, it appeared justified to assume that the intervals between consecutive infusions are sufficiently long to ensure that ECG measurements immediately prior to an infusion were not influenced by the previous administration. As such,

each infusion of volasertib is considered as 1 single drug administration, independent of the length of the dosing interval, and each ECG recorded prior to an infusion is considered as baseline.

Baseline

Handling baseline is important in light of the fact that most results are defined by change from baseline analysis. Individual (or administration) baseline was defined as the mean of the triplicate ECGs taken at the time point closest to but prior to the start of each infusion (ie, each infusion has its own baseline). To account for random variability associated with the administration baseline, a second baseline definition was applied. Average baseline was defined as the mean of the administration baselines (ie, 1 common baseline was used per patient for all available infusions).

Pooling Strategy

Prior to the ECG analysis, data were pooled across all trials to define treatment groups. Particularly for treatment regimens involving low or high doses, the number of patients may be too small to ensure estimates with sufficient precision. Therefore, groups were further collapsed to include a reasonable number of patients.

The intended number of patients per treatment group aimed to achieve a projected length of the 2-sided 90% confidence interval (CI) of no more than 10 milliseconds (ms) at each time point (ie, the distance between the mean and the limits of the CI is no longer than 5 ms). The rationale for this choice was that a mean QTc change from baseline of around 5 ms is the threshold of regulatory concern, as evidenced by an upper limit of the 2-sided 90% CI around the mean effect on QTc of 10 ms.[2] The sample size calculation was eventually based on a length of 8 ms to add more certainty. Preliminary analyses revealed a standard deviation of 10 to 12 ms in QTcF change from baseline. Therefore, the sample size consideration was based on a standard deviation of 12 ms. Using these assumptions, a 2-sided 90% CI based on the t statistic for the difference in paired means has a half-length of no more than 4 ms around the observed difference in means with 99% coverage probability, when the sample size per group is 40. The calculation was performed using the commercial software nQuery Advisor Version 6.01 (Statistical Solutions, Ltd, Cork, Ireland).

A pooling strategy was prespecified for treatment groups that contain fewer than 40 patients in order to attain groups that are are as homogeneous as possible. The pooling was conducted depending on whether patients received

- volasertib as a monotherapy or in combination with other anticancer drugs
- volasertib as a 1- or 2-hour infusion duration
- dose strengths applied as initial treatment.

In a first step, all patients receiving a specific volasertib regimen (eg, combination, 1-hour infusion, and 350 mg) were pooled across all trials. Subsequently, the size of the treatment groups was checked and small groups were collapsed with neighboring dose groups resulting in, for example, a monotherapy, 1-hour infusion duration, ≤300-mg group. Volasertib combination partners were not distinguished, as these are not known to have a QT interval prolonging effect, and therefore were pooled according to the same principle. Table 1 displays the treatment groups that finally resulted after pooling by initial treatment.

Table 1. Number of Patients by Pooled Initial Treatment.

Description	Volasertib Dose, mg	Infusion Duration, h	Number of Patients
		Volasertib monotherapy	
Low-dose 1-h monotherapy	≤300	1	87
High-dose 1-h monotherapy	≥350	1	58
Low-dose 2-h monotherapy	≤250	2	48
High-dose 2-h monotherapy	≥300	2	241
Total			434
		Volasertib combination therapy	
Low-dose 1-h combination therapy	≤300	1	74
High-dose 1-h combination therapy	≥350	1	386
Low-dose 2-h combination therapy	≤250	2	50
High-dose 2-h combination therapy	≥300	2	67
Total			577
Volasertib overall total			1011
		Placebo + LDAC	
Placebo 1-hour infusion	–	1	164

Abbreviation: LDAC, low-dose cytarabine.

Patients with dose modifications during the trials were analyzed for each infusion according to their actual dose administered.

Linear Mixed-effects Model for Repeated Measures Data

The primary endpoint, change in QTcF interval between administration baseline and multiple time points following the first intravenous infusion of volasertib, was analyzed by a linear mixed-effects model for repeated measures data.

This model included effects accounting for the following sources of variation: treatment and time as fixed categorical effects; the interaction effect treatment-by-time, as well as the fixed continuous covariate administration baseline.

An unstructured covariance structure was used to model the variability of the within-patient measurements. This type has the advantage that no assumptions are made about the within patient variability; as such, it is the most "liberal" as it allows every term in the variance-covariance matrix to be different. The SAS MIXED procedure was used, involving the restricted

maximum likelihood estimation method, and the Kenward-Roger method that is employed to adjust standard errors and estimate denominator degrees of freedom.

Adjusted means for treatment-by-time and 2-sided 90% CIs based on the *t* distribution were computed.

The endpoint change in QTcF interval from administration baseline to end of infusion over all available infusions was analyzed using the same approach as described above, except that the effect time was replaced by the number of infusion.

The number of infusions a patient receives (ie, the treatment duration) is expected to vary considerably across patients. The decision of whether the nth infusion was included in the repeated measures analysis was based on the same criterion as described above (see pooling strategy). This means that infusions were only included as long as evaluable data in QTcF change from baseline from at least 40 patients in any of the treatment groups were still available.

The repeated measures analysis was also applied to respective endpoints derived for HR, QT interval, PR interval, and QRS complex. All analyses were performed without adjustment for multiplicity.

Exposure-Response Analyses

Exposure-response modeling is a valuable approach to complement the statistical analysis of central tendency of QTc prolongation, particularly as it is not dependent on the dose strength and infusion duration. To establish the concentration-effect relationship, all data from patients treated with a volasertib monotherapy infusion (regardless of the infusion duration) were pooled into a common volasertib treatment group across trials.

The relationship between the volasertib plasma concentrations and the QTcF change from administration baseline was explored using a random coefficient model that involves a random intercept and a random slope for each patient.[10] Based on this relationship, the mean QTcF change from baseline and its 2-sided 90% CI was estimated at the geometric mean of the maximum plasma concentration (C_{max}) or other concentrations of interest.

These analyses were also performed using the corresponding endpoints based on the QT interval and HR.

Categorical Analyses

Categorical analyses based on the number and percentage of patients meeting or exceeding some predefined upper limits for absolute ECG intervals and change from baseline were conducted. The number of patients with

- QTc changes from baseline: $\leq$30 ms, >30 to 60 ms, >60 ms
- QT changes from baseline: $\leq$60 ms, >60 ms
- absolute QTc intervals: $\leq$450 ms, >450 to 470 ms, >470 to 500 ms, >500 ms
- absolute QT intervals: $\leq$500 ms, >500 ms
- PR changes from baseline: $\geq$25% and absolute value >200 ms
- QRS changes from baseline: $\geq$25% and absolute value >110 ms

was summarized.

The threshold of 470 ms was used to be consistent with the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0, which is widely accepted as a standard for describing and managing safety findings in clinical studies of anticancer therapy.[11] The other thresholds for QT/QTc are in accordance with the ICH E14 Guidelines,[2] whereas the thresholds for the PR and QRS changes were stated in correspondence received from the Food and Drug Administration (FDA).

Moreover, the number and percentage of patients with other morphologic ECG findings were summarized.

Sensitivity Analyses

Analyses that employ more than 1 infusion were also conducted using the average baseline (with the exception of the exposure-response analyses).

To provide further confidence in the results for the QTcF interval, the analyses were also applied to the corresponding endpoints based on the QTcN intervals.

The definition of administration and average baseline given earlier in this paper assumes that long-term treatment with volasertib does not result in a change in baseline over time because of a potential accumulation of volasertib. This assumption was checked by the following analysis. Absolute QTcF intervals recorded before the start of the volasertib infusions over all available cycles were analyzed by a linear mixed-effects model for repeated measures in a similar manner as for change in QTcF interval from administration baseline to end of infusion over all available infusions without the covariate administration baseline. Adjusted means for number of infusion and treatment-by-number of infusion along with 2-sided 95% CIs were computed. For the pairwise comparisons of the absolute QTcF intervals recorded before the start of the volasertib infusions, the differences between the expected means of absolute QTcF intervals before the second and subsequent infusions and absolute QTcF intervals before the first infusion were estimated by the difference in the corresponding least squares means along with 2-sided 95% CIs. Infusions were only included as long as predose QTcF interval data from at least 40 patients in any of the treatment groups were available.

In case of evidence that baseline values change over time, the results of the analyses involving the average baseline and QTcN endpoints, would require cautious interpretation.

Results

Volasertib monotherapy or combination therapy was found to prolong adjusted mean QTcF change from administration baseline in a clinically meaningful manner. The largest adjusted mean QTcF change from administration baseline

Table 2. Results of Repeated Measures Analysis of QTcF Changes From Individual Baseline Over Time Following the First Volasertib Infusion.

	QTcF Changes From Individual Baseline, ms							
	Volasertib Monotherapy				Volasertib Combination Therapy			
Time, h[a]	n	Mean (SD)	Adjusted Mean (SE)	2-sided 90% CI	n	Mean (SD)	Adjusted Mean (SE)	2-sided 90% CI
				Low-dose 1-h infusion (≤300 mg 1 h/m; ≤300 mg 1 h/c)				
EOI	53	17.25 (10.18)	16.95 (1.41)	14.63, 19.28*	67	15.65 (9.68)	16.03 (1.25)	13.98, 18.09*
1	52	12.43 (10.54)	12.19 (1.32)	10.01, 14.37	69	11.00 (8.98)	11.28 (1.15)	9.38, 13.18
4	48	8.79 (11.69)	8.70 (1.48)	6.25, 11.14	65	6.08 (8.92)	6.77 (1.28)	4.66, 8.89
24	48	−0.31 (10.26)	−0.35 (1.41)	−2.67, 1.97	64	−0.73 (10.63)	−0.51 (1.22)	−2.53, 1.50
				High-dose 1-h infusion (≥350 mg 1 h/m; ≥350 mg 1 h/c)				
EOI	40	30.48 (8.64)	31.73 (1.63)	29.06, 34.41*	51	19.66 (10.41)	20.44 (1.44)	18.07, 22.81*
1	40	21.30 (10.81)	22.46 (1.52)	19.96, 24.95	52	11.23 (10.14)	12.17 (1.33)	9.97, 14.37
4	41	14.05 (13.01)	15.33 (1.65)	12.62, 18.05	52	5.50 (10.96)	6.44 (1.46)	4.03, 8.84
24	41	0.05 (10.47)	1.33 (1.55)	−1.21, 3.88	51	1.11 (10.77)	2.03 (1.38)	−0.24, 4.31
				Low-dose 2-h infusion (≤250 mg 2 h/m; ≤250 mg 2 h/c)				
EOI	48	13.82 (9.16)	13.05 (1.49)	10.60, 15.49*	50	6.46 (7.77)	6.97 (1.45)	4.58, 9.36*
1	–	–	–	–	48	6.07 (9.05)	6.48 (1.37)	4.22, 8.74
6-8	48	3.76 (10.33)	2.99 (1.50)	0.52, 5.47	50	2.58 (11.25)	3.09 (1.47)	0.67, 5.51
24	48	2.18 (10.39)	1.41 (1.42)	−0.93, 3.76	50	−1.31 (9.85)	−0.79 (1.39)	−3.09, 1.50
				High-dose 2-h infusion (≥300 mg 2 h/m; ≥300 mg 2 h/c)				
EOI	236	16.90 (10.88)	16.55 (0.67)	15.45, 17.66*	67	15.83 (11.72)	16.07 (1.25)	14.00, 18.13*
1	81	12.20 (9.42)	11.39 (0.89)	9.91, 12.86	66	12.13 (10.86)	12.30 (1.18)	10.37, 14.24
4	154	8.35 (10.11)	8.44 (0.76)	7.18, 9.69	–	–	–	–
6-8	223	5.56 (9.86)	5.04 (0.69)	3.90, 6.17	65	4.41 (11.60)	4.97 (1.28)	2.85, 7.08
24	229	0.79 (9.88)	0.41 (0.65)	−0.67, 1.48	65	0.81 (10.82)	1.13 (1.22)	−0.87, 3.13

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error.
[a]Time points: EOI = end of infusion, 1 h = 1 hour after end of infusion, 4 h = 4 hours after start of infusion, 6-8 h = 6-8 hours after start of infusion, 24 h = 24 hours after start of infusion.
*Largest upper confidence limit of the 90% CI within treatment group.

(31.73 ms, 90% CI: 29.06, 34.41 ms) occurred at the end of infusion with the high-dose 1-hour monotherapy (Table 2). This group comprised dosage regimens of up to 550 mg volasertib. In comparison, the high-dose 1-hour combination therapy group (largest mean QTcF change from administration baseline: 20.44 ms, 90% CI: 18.07, 22.81 ms) included mainly patients with a dosing regimen of 350 mg volasertib (49 patients) and three patients receiving a dosing regimen of 400 mg volasertib. For all regimens, excluding the low-dose 2-hour combination therapy, the largest adjusted mean QTcF change from administration baseline exceeded the threshold of 10 ms for the upper limit of the 2-sided 90% CI.

The upper limit of the 90% CI for the largest mean QTcF changes from administration baseline exceeded the threshold of ≥20 ms (regarded as clinically relevant by Sarapa et al[4]), in the high-dose 1-hour monotherapy and combination therapy groups. This threshold was not exceeded in any other volasertib treatment group.

Integrated ECG analysis showed that the effects of volasertib on the mean QTc changes from baseline were transient and resolved within several hours after start of the infusion. At 4 hours (respectively 6 to 8 hours) after start of infusion, the upper limit of the 90% CI for the adjusted mean QTcF changes from administration baseline no longer exceeded the threshold of 10 ms (except for low- and high-dose 1-hour monotherapy). This may indicate that the QTcF-prolonging effect was no longer of relevant magnitude at these time points. At 24 hours after the start of infusion, the 90% CI included zero across all treatment groups, indicating that the QTcF increases from administration baseline had resolved.

As an example, Table 3 presents an analysis of QTcF changes between baseline and the end of infusion over time following multiple infusions of volasertib. The high-dose 1-hour combination therapy group was selected as it contained ≥40 patients across 11 infusions, whereas all of the other groups had fewer than 40 patients. Adjusted mean changes in QTcF interval at the end of infusion were comparable between results obtained for the first infusion (Table 2) and multiple infusions (Table 3). Placebo plus LDAC increased the QTcF interval slightly but not to a clinically relevant extent. Multiple infusions of volasertib did not appear to impact QTcF in the long term, evidenced by QTcF prolongations remaining comparable despite multiple infusions. Furthermore, the analysis of absolute QTcF intervals recorded before the start of the

Table 3. Results of Repeated Measures Analysis of QTcF Changes (ms) Between Baseline and End of Infusion Over Time Following Multiple Infusions of Volasertib, High-Dose 1-Hour Combination Therapy (≥350 mg 1 h/c).

Number of infusions	N	Mean	SD	Adjusted mean	SE	2-sided 90% CI
1	373	18.95	(12.80)	19.65	(0.58)	18.69, 20.61
2	295	20.10	(12.45)	20.71	(0.67)	19.61, 21.82
3	206	18.13	(13.26)	19.11	(0.81)	17.78, 20.44
4	163	18.95	(13.18)	19.95	(0.92)	18.42, 21.47
5	124	17.85	(15.06)	18.92	(1.03)	17.22, 20.62
6	103	17.39	(13.48)	18.81	(1.09)	17.00, 20.61
7	80	16.31	(10.99)	18.43	(1.02)	16.75, 20.12
8	73	19.66	(13.02)	20.16	(1.31)	17.99, 22.33
9	49	17.46	(10.55)	17.91	(1.50)	15.43, 20.39
10	47	19.24	(11.66)	20.25	(1.50)	17.77, 22.74
11	40	19.43	(12.79)	20.50	(1.58)	17.88, 23.12

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error.

volasertib infusions provided no evidence that long-term treatment induces accumulating baseline QTcF values. A positive linear relationship could be established between the plasma concentrations of volasertib and the changes from administration baseline in QTcF interval. This integrated analysis was considered appropriate to assess the proarrhythmic risk following treatment with volasertib.

Discussion and Conclusion

The aim of the described analysis strategy was to characterize the magnitude of risk arising from the observed effect of volasertib on the QTc interval duration to support a risk-benefit assessment and appropriate safety information. It was not intended to show that the resulting upper 2-sided confidence limit of the maximum change from baseline is below a predefined threshold.

Morganroth et al recommend that a 10- to 20-ms QTc change (upper limit of the 1-sided 95% CI of placebo-corrected maximum change from baseline) be considered clinically relevant and that patients in this range, especially those with QT-related risk factors, be safeguarded with careful ECG assessment during treatment. Based on adequate benefit-risk evaluation, the authors suggest that higher tolerance limits for QT(c) prolonging effects may be acceptable for oncological drugs as they meet patients' particular medical needs.[12]

Volasertib therapy relevantly prolonged the mean QTcF changes from administration baseline. Across all treatment groups, the largest adjusted mean QTcF changes from administration baseline occurred at the end of infusion, declined rapidly thereafter, and approached baseline values at 24 hours after the start of infusion.

There was no evidence for a long-term impact of multiple infusions of volasertib on the QTcF interval.

We believe that the evaluation of the ECG effects, as described in this article, is adequate to characterize the ECG effects of volasertib with sufficient precision and can describe the cardiovascular risk profile of the compound. A limitation mainly affecting low or high doses might be that the estimation of the magnitude of QT/QTc-prolonging effects is based on pooled treatment groups rather than on exact dose levels. However, this is counterbalanced by the analysis of the concentration-effect relationship where the QT-prolonging effect can be predicted at concentrations of interest by interpolation. The drugs used in combination with volasertib are not known to affect the QT interval. This is supported by the results of these analyses, as combination treatment did not appear to increase the QT-prolonging effect more compared to volasertib alone.

Alternatively, a thorough QTc assessment in a stand-alone study (ie, a dedicated QT study as proposed by Sarapa et al[4] performed in a patient population) may be preferred for compounds without a previous signal for QT prolongation and for which no QT prolonging effect is to be expected. The approach described in this article is suggested when the results of preclinical and/or in vitro experiments show a potential QT effect or QT prolongation is a known class effect, resulting in the implementation of intensive ECG monitoring starting from early clinical development, which provides a large amount of ECG data (centrally evaluated) over a broad range of doses. Essential features to be harmonized across trials include (1) QT-related exclusion criteria and (2) the collection/timing of ECG recordings. On consultation with regulatory authorities, a dedicated QT study may be replaced by the here described integrated analysis of ECG data from available trials. Particularly, when a large QT/QTc-prolonging effect of a new compound is expected, the role of a placebo or a positive control may be of minor importance.[4] These considerations might also be useful for other investigational drugs treating life-threatening diseases for which QT risk assessment is required but a TQT study is not feasible and, therefore, an alternative approach is needed.

Which approach is eventually chosen or is the most appropriate will largely depend on the properties of the investigational drug.

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